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(54) Title: INJECTION MOLDING PROCESS FOR THE PREPARATION OF AN ORAL DELIVERY DEVICE FOR A PHARMACEUTICALLY ACTIVE AGENT

(57) Abstract: An injection moulding process for the preparation of an oral delivery device comprising a core which contains a pharmaceutically active agent, having a coating with one or more openings leading to such a core. The invention also relates to devices produced by the process, and to injection moulds suitable for performing the process.

providing, if necessary preparing, the core of the device comprising a pharmaceutically active agent;

locating said core within a mould cavity surrounding the core, said mould cavity defining the required dimensions of the outer coating and preferably also defining the required position, shape and dimensions of the one or more openings;

injecting a fluid mouldable material into said mould cavity;

allowing the material to set to thereby form the outer coating;

separating the formed device from the mould cavity.

The core may be prepared by compressing suitable ingredients for the core to form a compacted mass which comprises the core of the device (also referred to herein as "tablet core"). This may be prepared using conventional tablet excipients and formulation compression methods. Thus, the core would typically comprise the active agent or agents along with excipients that impart satisfactory processing and compression characteristics such as diluents, binders and lubricants. Additional excipients that may form part of the core of the device include disintegrants, flavourants, colorants and release modifying agents. Typically the active agent and excipients are thoroughly mixed prior to compression into a solid core. The core of the device can be formed by conventional tablet-forming processes such as wet granulation methods, dry granulation methods or by direct compression. The core can be produced according to any desired pre-selected shape such as bi-convex, hemi-spherical, near hemi-spherical, round, oval, generally ellipsoidal, oblong, generally cylindrical or polyhedral, e.g. a triangular prism shape.

A preferred shape of core is one which is generally of cylindrical shape having two opposite facing generally convex circular end faces. Such convex end faces may be of a generally part-spherical domed convex shape, or generally conical or frustro conical. Another preferred shape of core is a convex or of a bi-convex shape comprising two opposite-facing domed surfaces which are generally circular or elliptical in plan.

The term "near hemi-spherical" is intended to be construed in the manner described in US-A- 5,004,614. The term "cylindrical" is intended to include both true cylindrical shapes and distorted cylindrical shapes. Preferably the core is formulated into a bi-convex shape, e.g. having two domed opposite surfaces. If the core has corners, e.g. corners between cylindrical side surfaces and convex end surfaces, a rounded corner radius of ca. 1mm is preferred to assist flow of the fluid coating material during injection.

The core could be produced in a multi-layered (e.g. bi- or tri- layered) form.

The delivery device of the invention is most suitable as an oral delivery device, as it can conveniently be made in the shape and size of a pharmaceutical

processing conditions to achieve this are specified in the literature. For these reasons, it is believed that typical operational conditions would be between temperatures of 25 - 300°C, more typically 50 - 250°C and especially 50 - 150°C. Preferably the injection moulding pressure should be less than 6000psi (ca. 400-450 kg/cm^2) to avoid damage to a tablet core within the mould cavity, typically pressures of 200 to 1000 psi (ca. 14-70 kg/cm^2), more typically 400 to 600 psi (ca. 30-45 kg/cm^2) have been found suitable. Conversely the tablet core should be made of materials and using suitable conditions that the core can withstand such pressures within the mould without breaking or crumbling.

The material of the outer coating may be any material which blocks (either permanently of for a suitable time period) exposure of the core to an environmental fluid, e.g. a gastro-intestinal fluid, and is not removed by dissolution or otherwise disrupted before a predetermined duration for controlled, delayed or sustained release of the active material in the core has occurred. Alternatively, the coating material may be selected because of aesthetic considerations. Any pharmaceutically acceptable fluid mouldable material which exhibits thermoplastic properties can be used as an outer coating for the tablet core, and suitable materials include thermoplastic organic polymers. Those skilled in the art of injection moulding characterise the flow properties of polymeric materials according to a melt flow index which ranges from 1 g/10min (very poor flow) to 50 g/10min (very high flow). It has been found that materials that exhibit a melt flow index in the range of 15 – 30 g/10min are particularly suitable for use in this invention. Representative materials and their blends suitable for use as a coating material in this invention include those listed in US-A-5,004,614. Preferred coating materials include the polymethacrylate copolymers, natural waxes and lipids, and biodegradable polymers in general. Other suitable polymer materials include polyvinyl acetates, such as the 40 and 20 grades thereof, cellulose acetate, butyrate and phthalate, EVA (ethylene vinyl acetate) or HPC (hydroxypropyl cellulose), silicones, or copolymers of methacrylic acid, methylmethacrylate, and methyl acrylate, such as that known as 4135F, available from Röhm polymers, or a blend based on 4135F. 4135F comprises a methacrylic acid, methylmethacrylate, methyl acrylate copolymer in a typical ratio 25:65:10 with a dissolution threshold of pH greater than 7.2.

Accordingly in a further aspect, the present invention provides a device adapted for oral delivery of a pharmaceutically active agent, when made by a process as described herein. Typically such a device comprises a core which includes a pharmaceutically active agent covered by an outer coating which includes one or more openings communicating from the exterior of the device to the core characterised in that the outer coating is a polymeric material exhibiting a melt flow

a resilient internal member can apply a resilient pressure to a core when enclosed in the mould cavity to help to hold the core in place within the mould cavity. Also the ability of such a member to move slightly when it contacts a tablet core on closing the mould can help to relieve any pressures on the core which might tend to break the core, and can help the internal member to accommodate to variations in the size between tablet cores. Preferably the resilient mounting of such an internal member should be such as to apply a resilient pressure of up to 200psi (ca. 14 kg/cm^2) to the tablet core, or conversely to be resiliently moveable under such a pressure applied thereto.

It is also preferred to provide an internal member with a vacuum conduit passing therethrough to the outside of the mould, by which reduced pressure may be applied to a tablet core in contact with the member to assist in retaining the core in place in the mould. Suitably the vacuum conduit may pass through a resiliently mounted internal member as described above. Such a vacuum conduit may be useful both in moulds which close along a horizontal axis such that the reduced pressure prevents the cores from falling out of the cavity, and also moulds which close along a vertical axis so that the reduced pressure supplements gravity in holding the core in place.

Normally an injection mould has one fixed part and a second moving part which moves into contact with the fixed part to close the mould. Suitably the resilient member and any vacuum conduit could be on this fixed part.

For use with a mould as described above having an internal member it is preferred to provide the core with at least one small seating indentation of a shape generally corresponding to the part of the member that contacts the core, and so positioned on the core that when the mould encloses a tablet core, the member seats in the indentation. This can help to positively locate the core in the mould cavity and to secure the core in place in the mould cavity. In the above-described bi-convex core such an indentation may be located on one or both of the convex surfaces, e.g. the convex end surfaces of the generally cylindrical core. Such an indentation may be need to be at most 1.5 mm deep, and preferably for example may need to be only ca. 0.005 cm deep. Suitably such an indentation is tapered to be narrowest at its bottom, e.g. having a frustro-conical profile. The core may also be provided with one or more, preferably at least three small seating projections e.g. ribs, to engage with the inner surface of the mould cavity, e.g. with corresponding concavities therein, to assist in locating the core within the mould cavity. Such projections may be shaped to make only a point contact with the mould cavity so as to avoid resulting in the formation of any corresponding opening through the coating.

It will be appreciated that the required shape, size, number of openings and the geometric arrangement of openings required for the device can be readily achieved by a suitable arrangement of the shape, size, number and relative positions of the internal members(s) on the mould or mould part. Any single opening can be as fine as 0.1um and up to as large as a face of the tablet core e.g. 10mm. Typical openings would be in the range 0.5mm - 4mm. Preferably, the opening(s) of the device will comprise about 10 - 60 % of the total face area of the device. The opening may have any convenient shape, but is preferably rounded, e.g. substantially circular or elliptical.

For example, in one embodiment the device may comprise a core which is generally of cylindrical shape having two opposite facing substantially circular end faces or of a bi-convex shape comprising two opposite-facing domed surfaces which are generally circular or elliptical in plan, covered with an outer coating which generally conforms to the outer shape of the core, the coating having two opposite facing openings therein communicating with substantially the centre of each of said respectively substantially circular or domed surfaces.

The injection moulding process of this invention can be used to produce a device which can be used for immediate, delayed or sustained release, for example to achieve release of the active agent at a pre-determined part of the gastro-intestinal tract. Those skilled in the art, when considering the release profile of a device containing an active agent, would consider factors such as drug solubility, the surface area and number of openings, coating thickness and the tablet core formulation properties. It will be appreciated that such variations in device can be readily accommodated by the process of this invention.

This process differs from known methods *inter alia* in that the coating is applied to create the device in a single operation i.e. no further processing of the coating is required such as mechanical drilling of the coat to expose the core. It permits an improved method of producing devices with a varying number, size and shape of openings. Moreover, the accuracy of opening size is more reproducible. It is believed that this process is more robust and simpler to operate than known methods and is particularly suitable for mass production of such devices.

The invention will now be described by way of example only with reference to the accompanying drawings.

Figs. 1 to 3 schematically shows sequential stages in the use of the process to make a device in accordance with this invention.

Figs. 4 and 5 show a device as made using the process of this invention.

Fig. 6 shows a preferred injection mould for the process of the invention.

Fig. 7 shows a preferred shape of tablet core.

mould part 20A (the clearance in the channel 25 between the part 24A and the mould part 20A is exaggerated for clarity). The resilient mounting of the projection 24A is such as to move under a downward pressure of ca. 200 psi from a tablet core (not shown) bearing thereon. Passing through projection 24A is a vacuum conduit 26, via which a partial vacuum can be applied to such a tablet core resting on projection 24A downwards. There is an injection gate 27 in the lower fixed mould part 24A for injection of fluid coating material.

Referring to Fig. 7 a preferred tablet core shape 71 is shown in plan (Fig. 7A) and in side view (Fig. 7B). The shape is generally cylindrical, with a cylindrical part 72 having spherically domed convex end faces 73, 74. In each face 73, 74 is an indentation 75, 76 of a profile each matching the convex frustro-conical profile of the projections 24A, 24B of the mould 20. The slope of the conical sides of these indentations is ca 35° relative to the longitudinal cylindrical axis of the core 71. The diameter of the outer rim of each indentation 75, 76 is ca. 70-75% of the overall diameter of the cylindrical shape, and the depth in the longitudinal direction is ca. 0.4 mm.

Example 1

The following tablet cores were formed by conventional means by mixing together the active ingredients with excipients and compressing to form the tablet core. These examples are intended to be by way of illustration rather than limitation.

Tablet core a) represents a core that is suitable for use in an immediate release formulation which consists of 10% active ingredient, 60% microcrystalline cellulose, 24% lactose, 5% starch glycolate (disintegrant) and 1% magnesium stearate (lubricant).

Tablet b) represents a core that is suitable for use in a controlled release formulation which consists of 10% active ingredient, 40% hydroxypropylmethyl cellulose (HPMC), 24% lactose, 20% microcrystalline cellulose, 5% starch glycolate and 1% magnesium stearate.

The coating material used was a low density polyethylene produced by Exxon Chemical. The grade was LD600BA natural. This material demonstrates a wide range of processing temperatures (160 to 240°C) and has a melt flow index of 20.5 g/10min. Operating conditions utilised were 150°C and pressure of 400psi.

The injection moulding machine used was a 35T Arburg.

The tablet cores shown in Figs 1 to 5 and 7 typically had a diameter of 8mm. The coating had a thickness, as defined by the gap in the cavity between the core and the inner wall of the cavity of ca. 0.5mm. The openings 7 in the coating were typically

Claims:

1. A process for the preparation of a device comprising a core which includes a pharmaceutically active agent covered by an outer coating which includes one or more opening communicating from the exterior of the device to the core characterised in that the outer coating is applied by injection moulding said coating around said core.

2. A process according to claim 1 which comprises;
providing a core of the device comprising a pharmaceutically active agent;
locating said core within a mould cavity surrounding the core, said mould cavity defining the required dimensions of the outer coating and also defining the required position, shape and dimensions of the one or more opening;
injecting a fluid mouldable material into said mould cavity;
allowing the material to set to thereby form the outer coating;
separating the formed device from the mould cavity.

3. A process according to claim 1 or 2 wherein a moulding pressure less than 400-450 kg/cm^2 is used.

4. A process according to claim 2 or 3 wherein the mould has a cavity in which the tablet core may be located with a space around the said core to define the required shape and dimensions of the coating, with one or more internal member extending from the interior surface of the mould cavity to abut the said core and to define the shape and position of the said one or more opening.

5. A process according to claim 4 wherein one or more internal member is resiliently mounted so as to be able to move reciprocally resiliently inward and outward relative to the mould cavity.

6. A process according to claim 5 wherein the resilient mounting of the internal member is such as to apply a resilient pressure of up to 14 kg/cm^2 to the tablet core, or to be resiliently moveable under such a pressure applied thereto.

7. A process according to claim 5, 5 or 6 wherein an internal member is provided with a vacuum conduit passing therethrough to the outside of the mould, by which reduced pressure may be applied to a tablet core in contact with the member to assist in retaining the core in place in the mould.

17. A device according to any one of claims 10 to 16 wherein the outer coating generally conforms to the outer shape of the core, the coating having two opposite facing openings therein.

18. A device according to any one of claims 10 to 17 wherein the core has a seating indentation of a shape generally corresponding to the part of an internal member of the mould that contacts the core, and so positioned on the core that when the mould encloses the tablet core the member seats in the indentation.

19. A device according to any one of claims 10 to 18 wherein the core has one or more seating projection to engage with the mould cavity.

Fig.6.

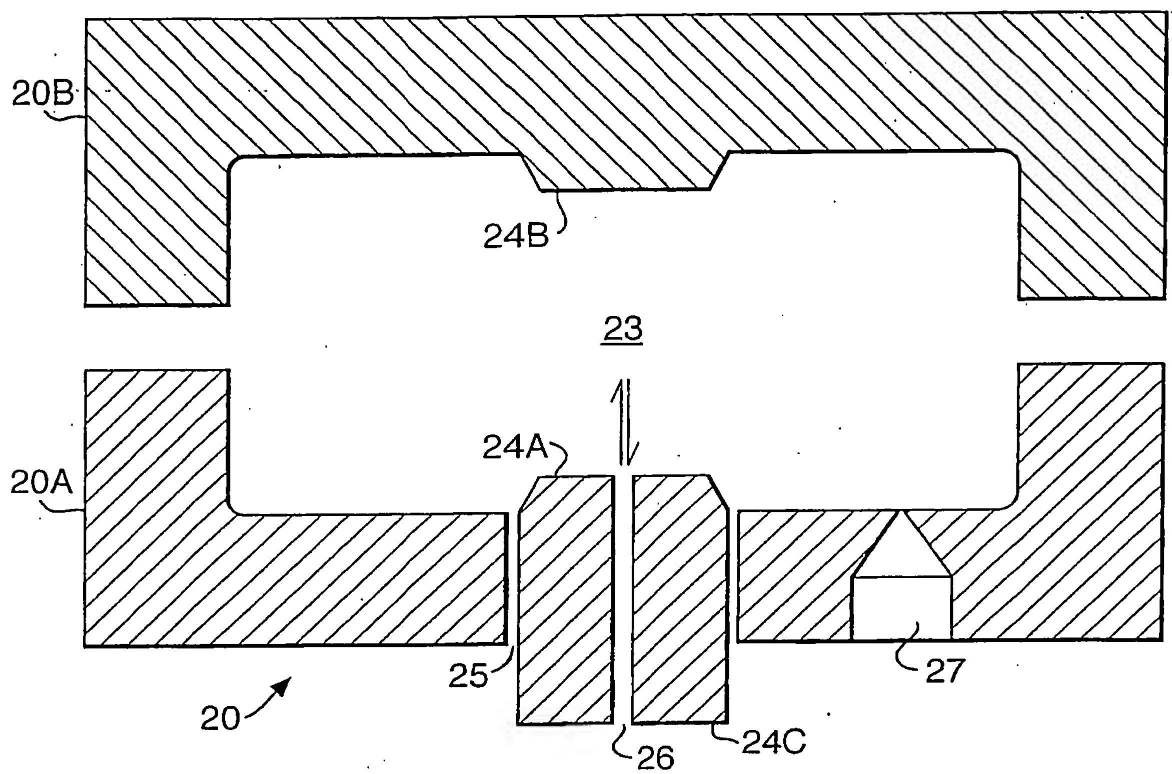
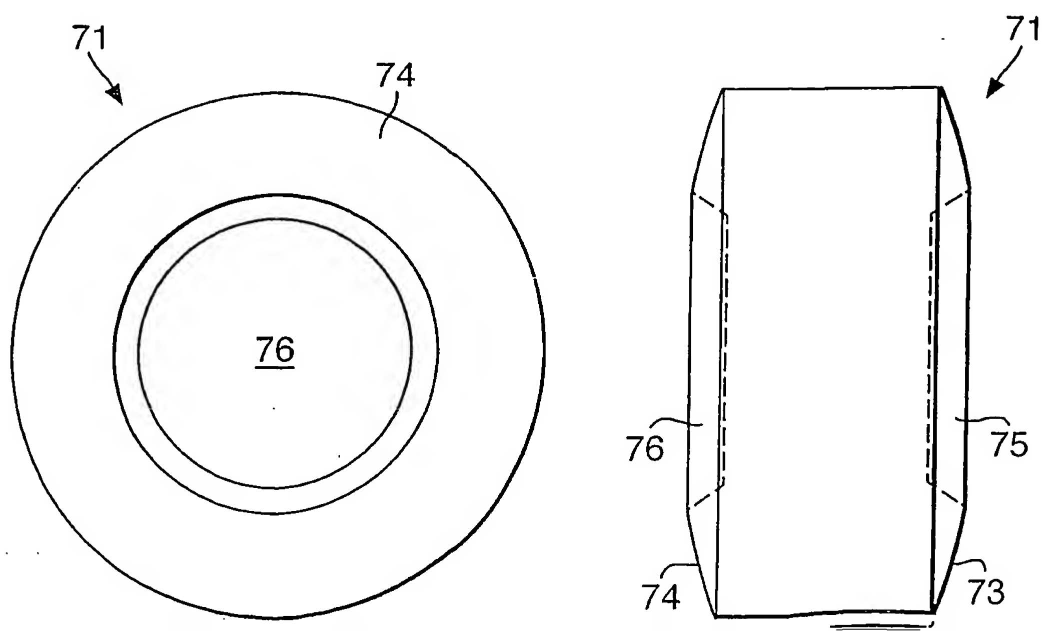


Fig.7.



C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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INTERNATIONAL SEARCH REPORT

Information on patent family members

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